# PATENT COOPERATION TREATY



# PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference P700PC00 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/DK 03/00919 | International filing date *(day/month/year)* 19.12.2003 | Priority date *(day/month/year)* 20.12.2002 |
| International Patent Classification (IPC) or both national classification and IPC A61K38/18 | | |
| Applicant AARHUS UNIVERSITET et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 17.06.2004 | 24.03.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Fayos, C Telephone No. +49 89 2399-2180 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00919

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

| | |
|---|---|
| 1-7, 9-50 | as originally filed |
| 8 | received on 06.02.2004 with letter of 06.02.2004 |

**Claims, Numbers**

| | |
|---|---|
| 1-71 | received on 19.01.2005 with letter of 19.01.2005 |

**Drawings, Sheets**

| | |
|---|---|
| 1/7-6/7 | as originally filed |
| 7/7 | received on 06.02.2004 with letter of 06.02.2004 |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

   **see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☒ the entire international application,

   ☐ claims Nos.

   because:

   ☒ the said international application, or the said claims Nos. 52-54 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-71 are so unclear that no meaningful opinion could be formed *(specify)*:

   **see separate sheet**

   ☒ the claims, or said claims Nos. 1-71 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | - |
| | No: | Claims | - |
| Inventive step (IS) | Yes: | Claims | - |
| | No: | Claims | - |
| Industrial applicability (IA) | Yes: | Claims | - |

No: Claims -

2. Citations and explanations

**see separate sheet**

**Re Item I**
**Basis of the report**

1- New claims 1-71 do not go beyond the subject matter of the application as originally filed. In fact, the newly filed claims 1-71 only amount to editorial changes with no real changes having regard to the subject matter claimed.

**Re Item III**
**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

2- Claims 52-54 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3- As indicated in the international search report (see PCT/ISA/210), the search has been limited to those parts of the claims which appear to be clear, supported and disclosed, namely, those parts relating to the agents which have been specified in present claims 17-20 and 22-25.

According to Rule 66.1(e) PCT, no international preliminary examination will be carried out with regards to the subject matter which is not covered by the search report.

4- Independently of the above reasoning, it is submitted that claims 1-16, 21, 26, 33-45, 61-63, 67-71 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, without providing the technical features (agents which are to be used, defined in technical terms (e.g. structurally) are not indicated) necessary for achieving this result. In addition, there is no technical support in the description as required by Article 6 PCT, for all the possible agents encompassed by the claims. These claims lack also disclosure (Art. 5 PCT), since the skilled person, after reading the description, would not able to perform the invention **over the whole area claimed** without undue burden and without needing inventive skill. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds

with potentially limitless structural possibilities for the claimed activity.

The terms "binding to", "interfering with" and "modulating" do not provide the claimed agent with technical features. There are mere functional statements which do not provide the skilled person with information to carry out the invention over the whole area claimed without undue burden.

4.1- **These claims do not meet the requirements of Arts. 5 and 6 PCT. They are so called "reach-through" claims wherein protection is sought for embodiments not yet identified. No examples are disclosed in the application as originally filed for all the possible agents encompassed by the claims, hence no claims to such products nor their possible uses can be allowed.**

5- The present application provides no examples to technically support the claims, contrary to Art. 6 PCT: no examples have been provided that any of the compounds encompassed by the claims has indeed a therapeutic effect in the treatment of a disease, as alleged in the claims (only 3 agents have been tested - p75, TrkA and Sortilin - and none has been shown to be effective in the treatment of a disease).

6- Second medical use claims 1, 3-32, 45, 61-63, 69, as presently worded are not acceptable under Art. 84, EPC. The therapeutic application is functionally defined by a mechanism of action ("modulating the activity of at least one neurotrophin and / or a pro-neurotrophin") which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease) (C-IV, 4.2).

Only claims 2, 33-44 define a disease, and can therefore be assessed as "second medical use" claims. Present claims 1, 3-32, 45, 61-63, 69, in the way they are formulated, are to be understood as "first medical use" claims.

7- With regards to the claims which specify the diseases to be treated, it is to be noted that it appears contradictory that by both decreasing or increasing the activity of a neurotrophin and / or proneurotrophin (see claims 3-4), the same diseases can be treated. Because of the fact that these claims are dependent on claims 3-4, it can be understood that the claimed diseases can be treated by either decreasing the activity (claim 3) or increasing the activity (claim 4) of at least one neurotrophin and / or a

proneurotrophin. Because of their dependency to claim 1, (and therefore also to claims 3, and 4), the claims which specify a disease to be treated (e.g. claims 2, 33-44) do not meet the requirements of Art. 6 PCT.

8- Finally, it is noted that although claims 1, 46, 52, 55, 61, 64, 66, 67, 69, 70 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

9- In view of the above objections (Art. 5 and 6 PCT), no opinion is to be given with regards to the novelty, inventive step and industrial applicability of the subject matter of claims 1-71.

Claims

1. Use of an agent capable of
   (i) binding to a receptor of the Vps10p-domain receptor family and/or
   (ii) interfering with binding between a receptor of the Vps10p-domain receptor family and a neurotrophin and/or proneurotrophin and/or
   (iii) modulating the expression of a receptor of the Vps10p-domain receptor family;

   in the manufacture of a medicament for use in a method for treatment of a disease or disorder by modulating the activity of at least one neurotrophin and/or a pro-neurotrophin in an organism, such as an animal.

2. The use according to claim 1, wherein said medicament is for the treatment of a neurological disease or disorder, such as a neural disorder.

3. The use according to any of the preceding claims, wherein the modulation is a decrease of the activity.

4. The use according to any of claims 1-2, wherein the modulation is an increase of the activity.

5. The use according to any of the preceding claims, wherein the neurotrophin is selected from neural growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5).

6. The use according to claim 5, wherein the neurotrophin is NGF or BDNF.

7. The use according to any of the claims 1-4, wherein the pro-neurotrophin is selected from pro-NGF, pro-BDNF, pro-NT-3 or pro-NT-4/5.

8. The use according to claim 7, wherein the pro-neurotrophin is pro-NGF or pro-BDNF.

9. The use according to any of the preceding claims, wherein the animal is a mammal.

10. The use according to claim 9, wherein the mammal is a human being.

11. The use according to any of the preceding claims, wherein the receptor is selected from SorLA, Sortilin, SorCS1, SorCS-2, or SorCS-3.

12. The use according to claim 11, wherein the receptor is Sortilin.

13. The use according to any of the preceding claims, wherein the agent is selected from proteins, peptides, polypeptides, antibodies, antisense RNA, antisense-DNA or organic molecules, SiRNA.

14. The use according to any of the preceding claims, wherein the agent is capable of inhibiting binding of said neurotrophin or said pro-neurotrophin to the receptor.

15. The use according to any of the preceding claims, wherein the agent is capable of binding to an extracellular part of the receptor.

16. The use according to any of the preceding claims, wherein the agent is an antibody directed against, an extracellular part of the receptor, an intracellular part of the receptor, or a transmembrane part of the receptor.

17. The use according to claim 16, wherein the agent is an antibody directed against a peptide comprising a sequence having SEQ ID NO: 1 amino acid residues 612-740.

18. The use according to any of the claims 1-15, wherein the agent is a peptide comprising a sequence having SEQ ID NO: 1 amino acids 24-77 or a variant thereof, said peptide being capable of binding to the receptor.

19. The use according to claim 18, wherein the variant is selected from one or more of the following sequences: SEQ ID NO: 2 amino acid residues 29-81 (propart from SorLa).

20. The use according to claim 18, wherein the peptide comprises one or more of the following sequences SEQ ID NO: 6 amino acid residues 19-121 (propart for NGF), SEQ ID NO 7 amino acid residues 19-127 (propart for BDNF), SEQ ID NO: 8 amino acid residues 17-124 (propart for neurotrophin-3 (NT-3), SEQ ID NO: 9 amino acid residues 25-80 (propart for neurotrophin-4 (NT-4) or a fragment or a variant thereof, said peptide being capable of binding to the receptor.

21. The use according to claim 1 or 20, wherein the agent is a peptide comprising a Sortilin receptor-binding sequence of proNGF.

22. The use according to claim 20, wherein the agent is a peptide comprising the sequence SEQ ID NO: 6 amino acid residues 19-121 (the sequence from the pro-part of NGF) or a variant thereof, said peptide being capable of binding to the receptor.

23. The use according to claim 21, wherein the agent is a peptide consisting of the following sequence SEQ ID NO: 6 amino acid residues 19-121 (propeptide of proNGF).

24. The use according to any of the claims 1-15, wherein the agent is a peptide having the sequence of SEQ ID NO: 10 or SEQ ID NO: 11, or a fragment or a variant thereof, said peptide being capable of binding the receptor.

25. The use according to any of the claims 1-15 wherein the agent is a peptide comprising an NGF variant or a Sortilin-receptor binding fragment of said NGF variant.

26. The use according to claim 24, wherein the peptide is capable of binding Sortilin and stimulating the activity of the Sortilin receptor.

27. The use according to any of claims 1-13, wherein the variant is selected from one or more of the following sequences: SEQ ID NO: 2 amino acid residues 47-66.

28. The use according to any of claims 1-13, wherein the variant is selected from one or more of the following sequences: SEQ ID NO: 13

29. The use according to any of the claims 1-13, wherein the agent is a fragment or variant of RAP (receptor-associated protein – SEQ ID NO. 12)

30. The use according to claim 29, wherein said agent is from 20 to 60 amino acids and contains the preferred domain amino acid positions 219-323 of receptor-associated protein.

31. The use according to any of the claims 1-13, wherein the agent is a peptide comprising a sequence having SEQ ID NO: 1 amino acids 34-77 or a variant thereof, said peptide being capable of binding to the receptor

32. The use according to any of the claims 1-13, wherein the agent is a peptide comprising a sequence having SEQ ID NO: 1 amino acids 50-70 or a variant thereof, said peptide being capable of binding to the receptor.

33. The use according to claim 1, wherein the disease or disorder is selected from one or more of the following diseases or disorders: inflammatory pain, diseases or disorders of pancreas, kidney disorders, lung disorders, cardiovascular disorders, various types of tumours, psychiatric disorders or neuronal disorders.

34. The use according to claim 1, wherein the disease or disorder is selected from Alzheimer's disease, Parkinson's disease, Huntington's chorea, stroke, ALS, peripheral neuropathies, necrosis or loss of neurons, nerve damage to trauma, kidney dysfunction, injury, and the toxic effects of chemotherapeutics used to treat cancer and AIDS, aberrant sprouting in epilepsy, schizophrenia, pancreas or lung injury and/or dysfunction, injury and/or dysfunction of the central and/or peripheral nervous systems.

35. The use according to claim 1, wherein the disease or disorder is selected from peripheral neuropathy, distal sensorimotor neuropathy, or autonomic neuropathies, such as reduced motility of the gastrointestinal tract or atony of the

urinary bladder, post-polio syndrome or AIDS-associated neuropathy; hereditary neuropathies, such as Charcot-Marie-Tooth disease, Refsum's disease, Abetalipoproteinemia, Tangier disease, Krabbe's disease, Metachromatic leuko-dystrophy, Fabry's disease, and Dejerine-Sottas syndrome, depression, mania or Down's syndrome.

36. The use according to claim 1, wherein said medicament is for the development, maintencence, or regeneration of neurons in an individual.

37. The use according to claim 1, wherein said medicament is for the treatment of nerves damage caused by any of the following: trauma, bums, kidney dysfunction or injury, pancreatic dysfunction or injury, lung dysfunction or injury, injury to fatty tissue, or the toxic effects of chemotherapeutics used to treat cancer and AIDS.

38. The use according to claim 1, wherein said medicament is for the treatment of a disorder of the central and/or peripheral nervous system that is associated with neuron degeneration or damage.

39. The use according to claim 1, wherein said medicament is for the treatment of any of the following: Alzheimer's disease, Parkinson's disease, Huntington's chorea, stroke, ALS, peripheral neuropathies.

40. The use according to claim 1, wherein said medicament is for the treatment of human neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, Huntington's chorea, Down's Syndrome, nerve deafness, and Meniere's disease.

41. The use according to claim 1, wherein said medicament is for the treatment of a motoneuron disorders, such as amyotrophic lateral sclerosis (Lou Gehrig's disease), Bell's palsy, and various conditions involving spinal muscular atrophy, or paralysis.

42. The use according to claim 1, wherein the disease or disorder is a neuropathy, such as peripheral neuropathy.

43. The use according to claim 1, wherein the disease or disorder is depression or mania.

44. The use according to claim 1, wherein said medicament is to be used as a cognitive enhancer, such as to enhance learning in individuals suffering from dementia or trauma.

45. The use according to any of the preceding claims, wherein the agent is administered in an amount of from 1 µg/kg to about 100 mg/kg per day.

46. An in vitro method for screening for a compound which alters the binding of at least one neurotrophin and/or a pro-neurotrophin to a receptor of the Vps10p-domain receptor family,

a) providing an assay for measuring the binding of a neurotrophin and/or a pro-neurotrophin to a receptor of the Vps10p-domain receptor family

b) adding the compound to be tested to the assay, and

c) determining the amount of a neurotrophin and/or a pro-neurotrophin bound to the receptor of the Vps10p-domain receptor family, and

d) comparing the amount determined in step c) with an amount measured in the absence of the compound to be tested,

e) wherein a difference in the two amounts identifies a compound which alters the binding of neurotrophins and/or pro-neurotrophins to the receptor of the Vps10p-domain receptor family.

47. The method according to claim 46, wherein the neurotrophin or pro-neurotrophin is as described in any of claims 5-8.

48. The method according to any one of claims 46-47, wherein the receptor is as described in any of claims 11-12.

49. The method according to any one of claims 46-48, wherein the neurotrophin and/or pro-neurotrophin is capable of binding to an extracellular part of the receptor, an intracellular part of the receptor or a transmembrane part of the receptor.

50. The method according to any one of claims 46-49, wherein the receptor is expressed in a cell and/or presented on a cell plasma membrane.

51. The method according to claim 50, wherein the cell is selected from peripheral neurons, central neurons, primary cultures of neuronal cells, neuron-derived cell-lines and transfected cells capable of expressing and/or presenting a receptor of the Vps10p-domain receptor family.

52. A method for determining the effect of an agent on activity of neurotrophins and/or pro-neurotrophins in cells expressing a receptor of the Vps10p-domain receptor family, said method comprising the steps of

a) administering said agent to a mammal naturally expressing the receptor,

b) measuring the activity of neurotrophins and/or pro-neurotrophins in said mammal,

c) comparing the measurement of step b) with a measurement obtained in the absence of the compound to be tested,

d) wherein the difference in the two measurements identifies the effect of said agent on the activity of neurotrophins on cells presenting receptors of the Vps10p-domain receptor family.

53. The method according to claim 52, wherein said method further comprises administering said agent to a mammal lacking expression of said receptor.

54. The method according to claim 53, wherein said mammal only lacks expression of said receptor in one or more selected tissues.

55. A method for modulating the transport of at least one neurotrophin and/or pro-neurotrophin out of, into or within a cell line expressing a receptor of the Vps10p-domain receptor family,

comprising administering a sufficient amount of an agent capable of binding a receptor of the Vps10p-domain receptor family.

56. The method according to claim 55, where the modulation comprises an increase in the anterograde transport of the neurotrophin and/or pro-neurotrophin in the neuron.

57. The method according to claim 55, where the modulation comprises a decrease in anterograde transport of the neurotrophin and/or pro-neurotrophin in the neuron.

58. The method according to claim 55, where the modulation comprises an increase in the retrograde transport of the neurotrophin and/or pro-neurotrophin in the neuron.

59. The method according to claim 55, where the modulation comprises a decrease in retrograde transport of the neurotrophin and/or pro-neurotrophin in the neuron.

60. The method according to any one of claims 55-59, wherein the agent is as defined in any of the claims 1-32.

61. Use of an agent capable of binding a receptor of the Vps10p-domain receptor family in the manufacture of a medicament for use in a method for treatment of a animal by modulating the transport of at least one neurotrophin and/or pro-neurotrophin out of, into or within a cell expressing a receptor of the Vps10p-domain receptor family in said animal, said method comprising administering to said animal a sufficient amount of said agent.

62. The use according to claim 61, wherein said agent is as defined in any of claims 1-32.

63. The use according to any of claim 61-62, wherein said modulation is as defined in any of claims 56-59.

64. A method of isolating a compound capable of altering the binding of at least one neurotrophin and/or proneurotrophin to a receptor of the Vps10p-domain receptor family comprising the steps of

a) screening a compound as defined in any of claims 46-60
b) selecting a compound altering the binding of at least one neurotrophin and/or pro-neurotrophin to a receptor of the Vps10p-domain receptor family,
c) isolating the compound of step b).

65. The method of claim 64 further comprising the step of refining the isolated compound/reducing the toxicity of the isolated compound.

66. A method of producing a pharmaceutical composition comprising the steps of claims 64 or 65 and further the step of formulating the refined compound/-compound with reduced toxicity with a pharmaceutically acceptable carrier or diluent.

67. Use of an agent as defined in any of claims 17-32 for the preparation of a medicament.

68. The use according to claim 67; wherein said agent is a soluble receptor of the Vps10p-domain receptor family or a fragment or a variant thereof.

69. Use of a soluble receptor of the Vps10p-domain receptor family or a fragment or a variant thereof for the preparation of a diagnostic agent for the diagnosis of neurotrophin and/or pro-neurotrophin related diseases.

70. A pharmaceutical composition comprising an agent as defined in any of claims 17-32 and a pharmaceutically acceptable carrier.

71. The pharmaceutical composition according to claim 70, wherein said agent is a soluble receptor of the Vps10p-domain receptor family or a fragment or a variant thereof.

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